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Original Article

Is It Useful to Administer Probiotics Together With Proton Pump Inhibitors in Children With Gastroesophageal Reflux?

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Background/Aims
Gastroesophageal reflux disease (GERD) is a frequent condition diagnosed in children and treated with proton pump inhibitors (PPI). Long-term PPI administration can alter intestinal bacterial population by suppressing the gastric acid barrier and may cause diarrhea. The aim of this study is to evaluate the prevalence of small intestinal bacterial overgrowth assessed by glucose hydrogen breath test among children that received 12 weeks of PPI with or without probiotics (*Lactobacillus reuteri* DSM 17938) associated, compared to controls.

Methods
Glucose hydrogen breath test was performed before PPI treatment and after 12 weeks of PPI treatment to 128 consecutive children with GERD (1-18 years old) and a control group (120 healthy children). The children with GERD were randomized into 2 groups: placebo group (64 who received PPI and placebo for 12 weeks) and probiotics group (64 who received PPI and probiotics for 12 weeks).

Results
After 12 weeks of treatment, dysbiosis was detected among 56.2% of children from placebo group (36/64), compared to 6.2% of children from the probiotics group (4/64, $P < 0.001$). Bacterial overgrowth was detected in 5% of controls (6/120). Probiotics group had a lower prevalence of dysbiosis, similar to controls ($P = 0.740$).

Conclusion
Probiotics administration decreased the rate of dysbiosis among children treated with PPI.
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Key Words
Breath tests; Child; Dysbiosis; Probiotics; Proton pump inhibitors

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Introduction

In children, gastroesophageal reflux disease (GERD) is considered when the retrograde flow of acid gastric contents into the esophagus induces severe symptoms and/or associated complications such as esophagitis or pulmonary aspiration.[1] A 4-week trial of antacid secretory agent—histamine H_2 receptor antagonists or proton pump inhibitors (PPI) is recommended for pediatric patients who are unable to describe their symptoms (infants, toddlers, young children, and those with neurodisability and communication difficulties) who have overt regurgitations and feeding difficulties, distressed behavior or failure to thrive.[1] PPI treatment has became the first line therapy prescribed nowadays for children older than one year old and adult patients with GERD.

Several studies have implicated PPI administration in the pathogenesis of small intestinal bacterial overgrowth (SIBO).[2,3] Use of PPI could predispose individuals to achieve SIBO by altering the intraluminal environment and bacterial flora. There is controversy regarding the risk of SIBO among PPI users because of conflicting results from prior studies.[3,4] For several reasons, the composition of the intestinal microbiota can be altered, so that bacterial overgrowth may occur. As the normal upper small bowel harbors less than 10^4 colony forming units (CFU)/mL and the vast majority of these bacteria are Gram positive aerobes, it is possible to define SIBO as any conditions differing from this.[5] SIBO is usually defined as a total growth of 10^5 CFU/mL in intestinal fluid.[6,7] Affected patients may be asymptomatic or have non-specific symptoms, such as bloating, abdominal pain, diarrhea, steatorrhea, flatulence, dyspepsia, nutrient malabsorption, weight loss, and failure to thrive.[8]

Glucose hydrogen breath test (GHBT) is one of the diagnostic methods used for SIBO detection.[5] Glucose is a monosaccharide that under normal circumstances is completely absorbed in the small intestine.[5] In case of bacterial overgrowth in the small intestine, the bacterial fermentation will take place at this level and the process of absorption and fermentation will be competitive.[6] These are the facts that supported the implementation of GHBT for the diagnosis of SIBO in clinical practice.

The aim of this study is to evaluate the prevalence of SIBO assessed by GHBT among children with GERD that received 12 weeks of antacid secretory agent treatment, compared to controls. We also analyzed the effect of simultaneous probiotic (*Lactobacillus reuteri* DSM 17938) administration to PPI treatment on reducing the rate of SIBO in children with GERD and monitored the intestinal symptoms in children with GERD treated with PPI and probiotics versus PPI and placebo.

Materials and Methods

The Basal Characteristics of Subjects

Between January 2014 and January 2017 the authors conducted a 3-year prospective study at an academic referral pediatric center in the Western part of Romania. GHBT was performed in 248 consecutive children (1-18 years old, mean age 8 ± 2.2 years). The inclusion criteria were as follows: 128 consecutive children with GERD treated with PPI for 12 weeks and 120 consecutive healthy age and gender matched subjects. The diagnosis of SIBO in this study was based on a positive GHBT. The development of suggestive symptoms such as abdominal pain/discomfort, bloating, flatulence, diarrhea, weight loss, and/or absence of weight gain was further assessed. The presence of gastrointestinal (GI) symptoms was assessed using a questionnaire with a Likert scale of symptom severity.[2] The questionnaires were administrated to parents/caregivers of pediatric patients aged below 8 years old and to children themselves in subjects older than 8 years old with optimal cognitive capacity. The questionnaire referred to the GI symptoms over the past 7 days. Each question was rated on a 5-point Likert scale from 0 to 4. Higher values indicated more severe symptoms. The authors used the Bristol stool scale chart[9] to assess the stool consistency. The exclusion criteria were as follows: recent gastroenteritis, laxative administration, anti-diarrheal medication, use of antibiotics in the month preceding the study, use of prednisone, drugs that alter intestinal motility, children suffering from diabetes, thyroid disease, pseudo-obstruction, and children who had undergone colonoscopy or enema in the last 4 weeks prior the enrollment.

Classification of the Subjects

GERD in children was diagnosed based on the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines,[10] that is mainly based on history and physical examination. Routine laboratory investigations were performed in all cases and only selected cases were referred to upper digestive endoscopy and/or combined esophageal pH and impedance monitoring. One hundred and twenty-eight children with GERD who received PPI for 12 weeks were consecutively randomized by a hospital based intranet computer system into 2 groups: placebo group (64 who

received PPI and placebo for 12 weeks) and probiotics group (64 who received PPI and probiotics for 12 weeks). *L. reuteri* DSM 17938 was administered to the probiotics group. The probiotics group received 5 mL bottles with odorless and tasteless oral solution. The recommended dose was 5 drops once per day containing 0.1×10^9 CFU. In the placebo group, the children received water bottled in 5 mL vials with a plastic dropper. The recommended dose was the same: 5 drops once per day. The PPI treatment in children with GERD consisted of esomeprazole 1 mg/kg daily, once per day (maximum 40 mg) for 12 weeks. GHBT was performed using LactoFAN analyzer (Fischer ANalysen Instrumente GmbH, Leipzig, Germany) before treatment and after 12 weeks of treatment for every child included into the placebo and probiotics group, and only once at enrollment for controls.

Diagnostic Method of the Glucose Hydrogen Breath Test

For measuring hydrogen concentrations in breath, the authors used LactoFAN device (Fischer ANalysen Instrumente GmbH, Leipzig, Germany). Before the test, children (except toddlers) were asked to brush their teeth and rinse the mouth with antiseptic mouth wash and tap water, to eliminate an early hydrogen peak due to action of oral bacteria on glucose substrate. After an overnight fast, 1 g/kg with a maximum of 50 g glucose, dissolved in 200 mL of water was orally administered to each tested child, according to the manufacturer's recommendations. An end-expiratory breath sample was collected immediately before and at every 20 minutes for the next 120 minutes after substrate intake. If the basal value of breath hydrogen was more than 16 ppm, it was considered a high value. The glucose was not administered in such situations and the test was rescheduled to be repeated with proper preparation. An increase in breath hydrogen in 2 consecutive measurements of at least 15 ppm above the basal value was considered indicative for SIBO, according to the manufacturer's recommendations.

Statistical Methods

The statistical analysis was performed using SPSS Statistics for Windows, version 17 (IBM Corp, Armonk, NY, USA). Means and standard deviations were calculated for numerical variables with a normal distribution, whereas for variables with a non-normal distribution, medians and ranges were calculated. Qualitative variables were expressed as numbers and percentages. Chi-test (with Yates' correction for continuity) was used to compare proportions expressed as percentages. For all statistical analyses, a two-tailed *P*-value < 0.05 was considered significant.

Ethics

All legal guardians or parents of patients enrolled in this study signed a written informed consent prior to inclusion. Institutional ethical approval with number 1712 was obtained for this study. The work was conducted in compliance with Local Institutional Review Board for Human Subjects Research Committee requirements.

Results

The demographic data and other characteristics of the study groups (control group, healthy children; placebo group, PPI and placebo for 12 weeks; probiotics group, PPI and probiotics for 12 weeks) are presented in Table. The mean age of basal characteristics was not different among the groups (control group 8.3 ± 2.7 years old, placebo group 8.5 ± 2.4 years old, probiotics group 7.6 ± 2.1 years old). The gender distribution of the patients enrolled in this study was as follows: girls/boys ratio in control group 41/79, in placebo group 29/35 and in probiotics group 21/43. The mean body mass index did not present significant differences among the groups (control group 16.1 ± 2.1, placebo group 15.7 ± 3.0 and probiotics group 14.3 ± 3.1). The children with GERD did not associate any comorbidities. Children from placebo and probiotics groups received only the medication prescribed in the study protocol. The children included in the control lot did not receive any drug at the

Table. The Characteristics of the Study Groups

Parameters	Control group (n = 120)	Placebo group (n = 64)	Probiotics group (n = 64)
Mean age ± SD (yr)	8.3 ± 2.7	8.5 ± 2.4	7.6 ± 2.1
Gender (girls/boys)	41/79	29/35	21/43
BMI (kg/m^2)	16.1 ± 2.1	15.7 ± 3.0	14.3 ± 3.1
Comorbidities (%)	0	0	0
Other drugs intake besides those from study protocol (yes/no)	no	no	no

BMI, body mass index.

time of enrollment. The control subjects did not use PPI, antibiotics or probiotics in the last 4 weeks prior the enrollment (Table).

GHBT was successfully conducted in all enrolled subjects with a few exceptions. Five children with GERD from the placebo group had basal values of hydrogen more than 16 ppm. These patients were rescheduled to repeat the GHBT with proper preparation. All 5 children had a lower baseline hydrogen when they came the second time.

The overall frequency of SIBO was 0% when the GHBT was performed before treatment in both groups of children with GERD: the placebo group and the probiotics group. The prevalence of SIBO assessed by GHBT in controls was 5.0% (6/120; $P = 0.090$; risk ratio [RR], 1.05; 95% CI, 1.01-1.10). The results of positive GHBT in the control, placebo, and probiotics groups before treatment are depicted in Figure 1.

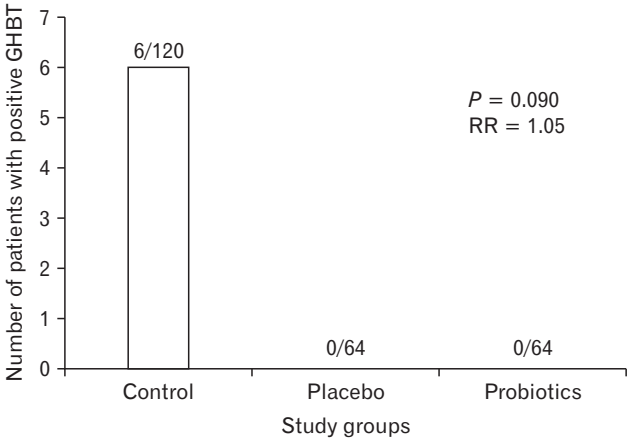

Figure 1. Glucose hydrogen breath test (GHBT) result of control, placebo, and probiotics groups before treatment. RR, risk ratio.

After 3 months of continuous PPI administration, SIBO was detected in 36 (56.2%) of the 64 children enrolled in the placebo group, versus 6 (5.0%) of the 120 children in controls ($P < 0.001$), with a RR of 2.17, 95% CI, 1.63-2.87). The results were statistically significant. Also, there was a significant difference between SIBO prevalence among the placebo group (36 patients [56.2%]) and the probiotics group (4 patients [6.2%]) ($P < 0.001$), with a RR of 2.14, 95% confidence interval (CI, 1.61-2.84). Only 4 (6.2%) of 64 children with GERD treated with simultaneous PPI and probiotics developed a positive GHBT after 12 weeks of treatment. Association of probiotics to esomeprazole significantly decreased the prevalence of SIBO among children with GERD compared to those treated with PPI and placebo ($P < 0.001$). Children with GERD treated with PPI and probiotics had a lower prevalence of SIBO, similar to control lot ($P = 0.740$). Figure 2 depicts the comparison and shows the statistical differences of SIBO prevalence as assessed by GHBT among the control, placebo, and probiotics groups after 3 months of PPI administration.

From the total of 36 children with GERD treated with PPI and placebo with positive GHBT after 12 weeks of treatment, 23 patients (63.8%) developed intestinal symptoms. These were considered as symptomatic children with SIBO. The rest of the 13 patients (36.1%) were free of symptoms, although they all had positive GHBT. All 4 children with GERD from the probiotics group with

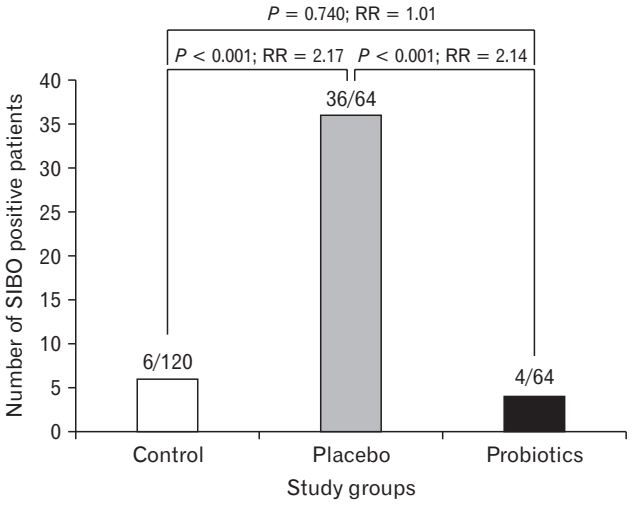

Figure 2. Comparison of small intestinal bacterial overgrowth (SIBO) prevalence as assessed by glucose hydrogen breath test among the study groups. RR, risk ratio.

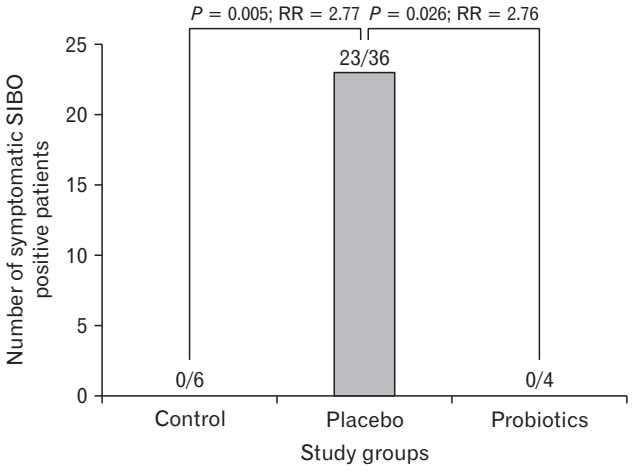

Figure 3. The presence of intestinal symptoms among different groups of children with positive glucose hydrogen breath test. SIBO, small intestinal bacterial overgrowth. RR, risk ratio.

positive GHBT after 12 weeks of treatment were symptom free. In these cases SIBO was diagnosed based on GHBT positivity only. There were significantly more symptomatic SIBO children among those treated with PPI and placebo compared to the probiotics group ($P = 0.026$; RR, 2.76; 95% CI, 1.79-4.27). All 6 subjects from the control group with positive GHBT were symptom free. Figure 3 shows the distribution of intestinal symptoms among the children with positive glucose hydrogen breath test from the control, placebo, and probiotics groups.

Discussion

There are several studies reporting different SIBO prevalence among children with different conditions. Siniewicz-Luzeńczyk et al[11] reported a prevalence of 63.0%, while a Dutch study conducted by Korterink et al[12] reported a lower prevalence of 14.3% among children with functional abdominal pain. Ojetti et al[13] reported the prevalence of SIBO in children with myelomeningocele and constipation as being 39.0%. Wang et al[14] found a prevalence of 31.0% for SIBO among children with autism spectrum disorders. The studies describing the relationship between SIBO and GERD are scarce.This is one of the few studies reporting SIBO prevalence among pediatric patients with GERD. In our study we described a higher prevalence of SIBO among children treated with PPI than previously reported.

Cares et al[15] assessed the risk of SIBO with chronic use of PPI in children and he found a potential risk of SIBO in chronic PPI users. However, Cares' results were not statistically significant. SIBO was detected in 5/56 (8.9%) PPI using group versus 1/27 (3.7%) control group ($P = 0.359$), with a relative risk of 2.4 in the above cited study.[15] Sieczkowska et al[16] also obtained a lower rate of intestinal dysbiosis (22.5% of 40 subjects treated for 3 months with PPI), compared to our results. Overall, from 128 children with GERD enrolled in our study and treated for 3 months with PPI (with or without associated probiotics), we found SIBO in 31.2 % of cases (40/128 children) versus 5.0% (6/120 controls) ($P < 0.001$; RR, 1.38; 95% CI, 1.22-1.56). Sieczkowska et al[16] reported that children with intestinal dysbiosis had higher prevalence of GI symptoms than those without SIBO, and the authors concluded that symptomatic patients undergoing PPI treatment should be evaluated for SIBO rather than empirically prolonging antisecretory therapy. A positive GHBT is highly suggestive for diagnosis of SIBO, but it is not always accompanied by the presence on intestinal symptoms. Therefore, the development of suggestive symptoms for SIBO in children with positive GHBT was assessed in our study. We found a high rate of symptomatic patients with SIBO (63.8% - 23/36 cases) among children with GERD treated with PPI, strengthening the conclusion of Sieczkowska et al[16] that symptomatic children taking PPI treatment should be tested for SIBO.

Hegar et al[17] studied the incidence of positive GHBT in a lot of children treated for one month with omeprazole and probiotics *Lactobacillus rhamnosus* R0011 and *Lactobacillus acidophillus* R0052 versus a group treated with omeprazole and placebo. There was no difference in the incidence of positive breath tests in the probiotics versus the placebo group (33.0% vs 26.5%; $P = 0.130$).[17] The above authors concluded that the probiotics tested did not decrease the risk to develop SIBO in children treated with omeprazole.[17] Hegar's results were contradictory compared to our study. We assessed the risk of SIBO after chronic use of esomeprazole in children and demonstrated a potential risk of SIBO when esomeprazole was continuously administrated for at least 3 months. Administration of probiotics *L. reuteri* decreased the risk of intestinal dysbiosis in our study. The frequency of positive GHBT in our study was significantly lower in the probiotics versus the placebo group (6.2% versus 56.2%; $P < 0.001$). The results achieved in our study compared to Hegar's research may be explained by different study design and methodology (longer period of PPI administration—3 months in our study compared to only 1 month in Hegar's study) and the different pediatric population enrolled.

Rosen et al[18] demonstrated that acid-suppression may favor gastric bacterial overgrowth of certain strains including *Staphylococcus* and *Streptococcus*. In the above mentioned study, the non-acid reflux was associated with greater concentrations of bacteria in the lung, increasing the risk of upper and lower respiratory tract infections.[18] Rosen's study had different methodology compared to our study. The authors did not use GHBT. Rosen's research was based on microbiota assessment using cultures from the pulmonary aspirates in patients with GERD treated with PPI that associated aspiration pneumonia. The results converged to a similar conclusion: antisecretory drugs contributed to the change of the individual GI microbiota among patients with GERD.[18]

Lyszkowska et al[19] demonstrated that administration of *Saccharomyces boulardii* for one month alleviated abdominal pain, bloating, flatulence among children with short bowel syndrome. Lyszkowska's study was conducted on a different pediatric population with short bowel syndrome, but the authors have demonstrated that *S. boulardii* induced changes in stool flora and may impact the gut microbiota. Our research focused on another probiotics strain, *L. reuteri*, and this strain also alleviated digestive symptoms among children with positive GHBT treated with PPI.

Liang et al[20] reported that 116 of 200 patients with GI malignancies (58.0%) were long-term PPI users and of these, 86 (74.1%) were positive for SIBO. The authors showed that the group receiving probiotic treatment (*Bifidobacterium*) and PPI had 19.0% SIBO-positive patients, whereas the group that was administered placebo and PPI showed 74.6% SIBO-positive patients.[20] SIBO prevalence reported by Liang et al[20] is higher compared to our study both in placebo and probiotics lot (56.2% and 6.2% respectively), but this Chinese research was conducted on adults patients with GI malignancies, that might increase the rate of intestinal dysbiosis. The clinical symptoms in the study by Liang et al[20] were much diminished in the probiotics group, and this difference reached statistical significance on comparison with the placebo arm of the study ($P < 0.05$). These results are similar to our report. In our study, there were 63.8% symptomatic SIBO children among those treated with PPI and placebo while in the probiotics group none of the 4 children with positive GHBT presented intestinal symptoms ($P = 0.026$). It could be a beneficial effect of probiotics association.

Other papers suggested that probiotics may enhance the efficiency of antibiotics for SIBO eradication.[21] One study showed that treatment with rifaximin along with probiotic *Lactobacillus casei* improved the symptoms of SIBO more effectively than the antibiotic followed by probiotics.[21] Our research sustained the beneficial effect of *L. reuteri* in preventing intestinal bacterial overgrowth among children treated with PPI. Based on the results of our study, in order to decrease the rate of SIBO, we recommend administrating probiotics based on *L. reuteri* to all children with GERD treated with long-term antisecretory medication. More studies, however, are needed to evaluate the efficacy of probiotics among children treated with PPI in relation to occurrence of SIBO.

Nowadays, hydrogen breath tests, using glucose or lactulose as substrates are the most common diagnostic tools for SIBO. Hydrogen breath tests with lactulose may be able to diagnose only one-third of patients with SIBO according to some authors.[22,23] Kerlin and Wong[24] have reported that GHBT performed for 2 hours had a sensitivity of 93.0% and a specificity of 78.0% in SIBO identification against the gold standard of a jejunal aspirate. Therefore, in this study the authors assessed SIBO by using glucose as the substrate for hydrogen breath tests. GHBT in our study identified all subjects with SIBO, except methane producing bacteria overgrowth.

There are some pitfalls in the interpretation of GHBT: since glucose is absorbed completely in the upper small intestine, it may not be able to diagnose SIBO of the distal small intestine.[22] Some studies described a considerable number of non-hydrogen producing bacteria, that produce other gases such as methane and hydrogen-sulfide and may not be detected with the hydrogen breath test, inducing false negative results for SIBO.[5,22] The discrepancy between GHBT positivity and presence of symptoms found in this study could also be explained by other sources of error. Delayed gastric emptying may cause false negative results, and rapid transit through the small bowel may produce false positive hydrogen breath tests. False positive results may also be due to the oral bacterial flora and in cases of non-compliance to follow to a low fiber diet 24 hours prior to the test.[5] Based on these observations, we may speculate that in our study some children with positive GHBT without any GI symptoms had false positive breath test results due to rapid small bowel transit. Oral flora contamination could not be a confounding factor for false positive results in our study because we have ensured rigorous oral hygiene in all children prior to inclusion, and all subjects followed a low fiber diet 24 hours prior to the test.

A limitation of this study is represented by the fact that we did not assess the methane concentration in exhaled breath air. Therefore, we may have missed the identification of certain non-hydrogen producing bacteria overgrowth. Another limitation of this study is the fact that we did not use jejunal cultures for SIBO assessment. Culture of the jejunal aspirate is recognized as the most direct method for diagnosing SIBO.[4] Yet, obtaining jejunal aspirates implies invasive procedures hardly accepted by parents in pediatric patients. In children with isolated distal SIBO, it could remain undiagnosed despite using jejunal cultures.[25] Due to all these disadvantages of jejunal aspirates, GHBT was used in this study as an indirect, but reliable alternative test to assess SIBO.[4,5,22]

In conclusion, the administration of probiotics not only decreased the rate of SIBO among children with GERD treated with PPI, but also significantly reduced the expression of digestive symptoms encountered in the group with positive GHBT. Being a disorder that requests long-term antisecretory therapy, GERD may benefit by acid suppression combined with probiotics in order to decrease the risk of intestinal bacterial alteration. Routine administration of the strain *L. reuteri* could be beneficial to all children with GERD treated with PPI in order to prevent SIBO. Nevertheless, PPI long-term administration in children should be avoided and "step-down" or "on demand" strategy should be implemented.

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Conflicts of interest: None.

Author contributions: Oana Belei conducted the study, contributed to the conception and the design of the study, to the

collection, analysis, and interpretation of data, and revised and approved the final version to be published; Laura Olariu contributed to the collection, analysis, and interpretation of data, and approved the final version to be published; Andreea Dobrescu drafted the manuscript, contributed to the collection, analysis, and interpretation of data, and approved the final version to be published; Tamara Marcovici contributed to the collection, analysis, and interpretation of data, and approved the final version to be published; and Otilia Marginean contributed to the collection, analysis, and interpretation of data, and approved the final version to be published.

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